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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
SINGH, ANOOP KUMAR	

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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,064	PELED ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *201, 209, 212-214, 239, 244 -248* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *201, 209, 212-214, 239, 244 -248* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/6/09; 2/5/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/05/2009 has been entered.

Applicant's amendment to the claims filed on February 5, 2009, has been received and entered. Claims 1-200, 202-208, 210-211, 215-238, 240-243 have been canceled, while claims 201, 212, 244-245 have been amended. Applicants have also added claims 246-248 that are generally directed to elected invention

Claims 201, 209, 212-214, 239, 244 -248 are pending in the instant application.

Election/Restrictions

Applicants' election of claims 201, 209-215, 217-231, 235, 238 and 239 (Group I) in the reply filed on October 25 was acknowledged. Applicants have also elected culturing the cells in presence of one copper chelator (claims 201), neonatal umbilical cord cells (claim 209), FLT-3 ligand (claim 212) and granulocyte colony-stimulating factor (claim 214) as election of species for the elected invention. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The restriction was deemed proper and therefore was made final.

Claims 201, 209, 212-214, 239, 244- 247 and 248 are under current examination.

Information Disclosure Statement

The IDS filed on 2/05/2009 and 4/6/2009 has been considered.

Withdrawn-Claim Rejections- 35 USC § 112

Claims 201, 209, 212-214, 239, 244 -245 were rejected under 35 U.S.C. 112, first paragraph. Applicants' amendments to the claims base claim is persuasive and instant specification enables one skilled in the art to make and/or use the invention directed to a method of expanding an *ex vivo* population of $CD34^+$, $CD34^+/CD38^-$ and $CD133^+$ hematopoietic stem cells in culture medium, while at the same time inhibiting differentiation of the said cell ex vivo in culture medium; said method comprising:(a) providing hematopoietic mononuclear cells that are not enriched prior to culturing; (b) culturing said mononuclear cells *ex-vivo* for a period of at least 14 days under conditions allowing for cell proliferation, said conditions comprising: (i) providing nutrients and a combination of early acting cytokine or cytokines; (ii) removing one half of the culture volume and replacing it with fresh medium and cytokines weekly; and, at the same time, culturing said mononuclear cells under conditions inhibiting differentiation of said hematopoietic stem cells, said conditions comprising providing an amount of tetraethylenepentamine (TEPA) effective in reducing intracellular available copper concentration in said cells; thereby expanding a population of said hematopoietic stem cells while at the same time inhibiting differentiation of said hematopoietic stem cells *ex-vivo* for a period of at least 14 days.

It is noted that claims have been amended to include the limitations of culturing the mononuclear cells in a combination of early acting cytokine, and an amount of TEPA effective in reducing intracellular copper concentration resulting in inhibition of differentiation of CD34+ cells for a period of at least 14 days, such

that one of ordinary skill in the art would be able to practice the method as claimed without extensive or undue experimentation.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 201, 209, 212-214, 239, 244-245 remain rejected under 35 U.S.C. 103(a) and newly added claims 246-248 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (Sheng Wu Gong Cheng Xue Bao. 2002, art of record) , 18(3):343-7, abstract) and Peled et al (WO/1999/40783, 8/19/1999, IDS).

In view of Applicants' amendment of base claim 201, introducing the limitation "removing one half of the culture volume and replacing with fresh medium and cytokine weekly", the previous rejections of claims 201, 209, 212-214, 239, 244-245 over Fietz et al and WO99/40783 document are hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. However, upon further consideration a new rejection is made that is presented in separately.

The rejection over Wang et al (Sheng Wu Gong Cheng Xue Bao. 2002 May; 18(3):343-7), in view of Peled et al (WO99/40783, 8/19/1999, IDS), set forth on pp. 8 of the previous office action dated November 6, 2008 is maintained for claims 201, 209, 212-214, 239, 244-245 and newly applied to 246-248 for reasons of record.

Applicants' arguments filed February 5, 2009 have been fully considered but are not persuasive. Applicants argue that Wang reports total cell proliferation of

MNCs for 4 weeks only, with poor results (50 fold increase versus >30,000 fold increase in CD34+ selected culture), poor CD34+ expansion for only 7 days in the unselected MNC cultures (50 + 33.2 fold). According to Wang, the results showed that CD34+ selected cells culture could obtain more CFU-GM cells. Applicants also assert that Wang is silent with regard to the re-feeding and reseeding of cultures. Thus, Applicants submit that the combination of Wang and Peled fail to teach or suggest all the limitations of the claimed invention, and as such, do not constitute *prima facie* evidence for obviousness. Further, Applicants submit that one of ordinary skill in the art reading the combination of Wang and Peled would have no reasonable expectation of success in reaching the claimed invention.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is relevant to point that the ultimate goal of expanding CD34+, CD34+/CD38- and CD133+ hematopoietic stem cells are to provide long term expansion of stem and early progenitor cells. As previously indicated, regarding claims 201, and 247, Wang et al describe a method for *in vitro* expansion of mononuclear cells (MNC) to expand hematopoietic stem and progenitor cells. Specifically, Wang et al teach providing hematopoietic MNC and culturing said MNC for a period of greater than 14 days in presence of a combination of cytokine including SCF, IL-3, IL-6, FLT-3 and TPO, thereby expanding the population of hematopoietic stem cell. It is noted that Wang et al reported that expanding Cd34+ in MNC for more than 50 fold. Thus, Wang et al teach a method of expanding CD34+ HSC from mononuclear cells. The deficiency of Wang is cured by Peled et al. who provided motivation to use TEPA as well as taught all the other limitations for a method of expanding CD34+, CD34+/CD38- and CD133+. To the extent that Wang et al. describe the expansion of CD34+ cells from the culture of MNC, the rejection

is applicable to the instant case. With respect to applicants' argument that Wang et al. is silent with regard to refeeding or reseeding, it is noted that such is supplied by the reference of Peled et al particularly since the rejections is based on combinations of references.

Applicants' selective reading of Peled et al. ignores the teachings of the reference of Peled et al. A person of skill in the art would be motivated to expand hematopoietic stem and or progenitor cells in presence of TEPA and also refeed and reseed cytokine containing medium, because the method would allow to expand CD34+ stem cell, while at the same time inhibiting the differentiation of the CD34+ cells for greater than 2 weeks, with a reasonable expectation of success. In the instant case, contrary to applicants' assertion, Peled et al. provide motivation as well as adequate guidance to one of ordinary skill in the art to include Copper chelator with early acting cytokine for expanding total number of cell, number of CD34+ cells and clonability (as evidenced by Peled see figure 1-3 and table 1). The results disclosed by Peled suggest that TEPA inhibits erythroid differentiation. Furthermore, Peled et al also teach that long-term cultures containing CD34+ cells are maintained for 3-5 weeks by weekly semi- depopulation (one half of the culture volume was removed and replaced by fresh medium and cytokines). Peled et al also disclose that hematopoietic stem cell may be obtained from neonatal cord blood (see page 20, line 7, limitation of claim 209). It is relevant to point out that addition of TEPA (0-50 μM, limitation of claims 244-245) resulted in a higher clonability in long-term cultures supplemented with either early cytokines (Figure 4) or both early and late cytokines (Figure 3, page 19, lines 20-21, 34-39, limitation of claims 212-214 and 248), as compared to cultures supplemented only with cytokines (See page 23 and 24, also see Figure 1, claims 1, 14-16). Peled et al. also contemplated the cells comprise committed progenitor cells and non-differentiated stem cells (see page 20, lines 10-11 and claim 17 of '783, limitation of claim 239). In fact, Peled et al. emphasizes that method would overcome the deficiency of expanding

hematopoietic stem or progenitor cells by using a series of chemical agents that bind (chelate) transition metals, that can inhibit (delay) the process of differentiation of stem cells as well as intermediate and late progenitor cells and thereby stimulate and prolong the phase of active cell proliferation *ex vivo* (emphasis added,). Peled et al assert that effect of Copper and other transition metals depletion could be used for maximizing the *ex vivo* expansion of various types of hematopoietic cells (see page 4, lines 12-18). It is also noted that Peled et al. teaches that method could be practiced with any hematopoietic cell and enrichment of hematopoietic CD34+ cells is only described as a preferred embodiments (see page 5, line 29).

Accordingly, in view of the teachings of Wang and Peled, it would have been obvious for one of ordinary skill in the art that method of expanding CD34+ cells was recognized as part of ordinary capability of one of skill in the art. One of skill in the art would have been capable of applying this known technique of expanding CD34+ cell, total number of cell and clonability to the known method of culturing unselected cells as in Wang. The results would have been predictable to one of ordinary skill in the art as Peled has already disclosed that Copper chelator TEPA in presence of low doses of early acting cytokine results in expansion in total number of cell, CD34+ cells and progenitor clonability in short as well as long term culture (more than 5 weeks, see figure 11 and 22). Therefore, given that copper chelator such as TEPA was available for use to expand long term culture by inhibiting/delaying the differentiation of CD34+ cells through chelation of transition metal as per teaching of Peled, it would have been obvious for one of ordinary skill in the art to use copper chelator TEPA in the culture medium disclosed by Wang with reasonable expectation of achieving predictable results of expanding CD34+ cell in culture of MNC. One who would practiced the invention would have had reasonable expectation of success because Wang had already described a method of *ex vivo* expansion of blood mononuclear cells (MNCs), in presence of early and late acting cytokine for one week, while Peled described use of copper chelator such as

TEPA that could facilitate expansion of CD34+ cells beyond one week by inhibiting differentiation of CD34+ cells. Thus, it would have only required routine experimentation to modify the method disclosed by Wang to include TEPA in the culture medium as required by instant invention. Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Applicants' argument of superior expansion of CD34+ cells is also not persuasive because any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Peled et al. teach that long-term culture of $CD34^+$ cell cultures in the presence of TEPA and the claimed combination of cytokines, thus the relevance of Applicants' arguments with respect to fold expansion is not apparent. Further, the expansion of hematopoietic cells by refeeding or reseeding is also described by Peled et al. Such methodology was considered routine in the prior art. Therefore the fact that hematopoietic cells may be expanded to a greater extent in presence of TEPA and specific combination of cytokine from a hematopoietic cell population irrespective of starting population is an expected result (higher expansion of HSC). As indicated in MPEP 716.02(c), Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977). "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Instant rejection is applied to address the issue of newly added limitation of culturing MNC for a period of at least 14 days by periodically replacing (semi depopulating the medium once every week) the culture medium with the fresh medium and cytokine.

Claims 201, 209, 212-214, 239, 244-248 are rejected under 35 U.S.C. 103(a)) as being unpatentable over Emerson et al (US Patent 5,437,994 dated 08/01/1995), and Peled et al (WO/1999/40783, 8/19/1999, IDS).

Claims are directed to a method of expanding *ex vivo* population of hematopoietic stem cell by (a) providing hematopoietic mononuclear cells that are not enriched prior to culturing; (b) culturing said mononuclear cells *ex-vivo* for a period of at least 14 days under conditions allowing for cell proliferation, said conditions comprising: (i) providing nutrients and or a combination of cytokines selected from the group consisting of thrombopoietin (TPO), interleukin 6 (IL-6), FLT-3 ligand, stem cell factor (SCF) and interleukin 3 (IL-3); (ii) removing one half of the culture volume and replacing it with fresh medium and cytokines weekly; and, at the same time, culturing said mononuclear cells under conditions inhibiting differentiation of said hematopoietic stem cells, said conditions comprising providing an amount of tetraethylenepentamine (TEPA) effective in reducing intracellular available copper concentration in said cells; thereby expanding a population of said hematopoietic stem cells while at the same time inhibiting differentiation of said hematopoietic stem cells *ex-vivo* for a period of at least 14 days.

Emerson et al teach a method of expanding *ex vivo* population of hematopoietic stem cell by providing hematopoietic mononuclear cells that are not enriched prior to culturing that are separated from bone marrow using a Ficoll-Paque density gradient centrifugation (see col. 25, line 16 and col. 27, line 25-26) containing HSC, (b) culturing said cell ex vivo in presence of liquid culture medium, wherein culture medium is replaced periodically and wherein the culture medium contains nutrient and cytokine including TPO, IL-6, FLT-3L, EPO, GM-CSF, IL-11, PDGF and EGF (see claims 1-20 of '994, limitation of claim 212 -214). It is also reported that the cells could be obtained form peripheral blood mononuclear cells, human bone marrow cells, human fetal liver cells, and human cord blood cells (see claim 6 of '994, limitation of claim 209).

While, Emerson teach a method of expanding *ex vivo* population of hematopoietic stem cell by culturing unselected hematopoietic mononuclear cell in presence of nutrient and cytokine beyond 14 days, but differed from claimed invention by not culturing MNC is presence of TEPA, thereby expanding a population of HSC.

The deficiency of Emerson is cured by Peled et al. who provided motivation to use TEPA as well as taught all the other limitations for a method of expanding CD34+, CD34+/CD38- cells. Peled et al. teach a method to expand HSC in presence of Copper chelator and early acting cytokine for expanding total number of cell, number of CD34+ cells and clonability (as evidenced by Peled see figure 1-3 and table 1). The results disclosed by Peled suggest that TEPA inhibits erythroid differentiation. Furthermore, Peled et al also teach that long-term cultures containing CD34+ cells are maintained for 3-5 weeks by weekly semi- depopulation (one half of the culture volume was removed and replaced by fresh medium and cytokines). Peled et al also disclose that hematopoietic stem cell may be obtained from neonatal cord blood (see page 20, line 7, limitation of claim 209). It is relevant to point out that addition of TEPA (0-50 μM, limitation of claims 244-245) resulted

in a higher clonability in long-term cultures supplemented with either early cytokines (Figure 4) or both early and late cytokines (Figure 3, page 19, lines 20-21, 34-39, limitation of claims 212-214 and 248), as compared to cultures supplemented only with cytokines (See page 23 and 24, also see Figure 1, claims 1, 14-16). Peled et al. also contemplated the cells comprise committed progenitor cells and non-differentiated stem cells (see page 20, lines 10-11 and claim 17 of '783, limitation of claim 239). In fact, Peled et al. emphasizes that method would overcome the deficiency of expanding hematopoietic stem or progenitor cells by using a series of chemical agents that bind (chelate) transition metals, that can inhibit (delay) the process of differentiation of stem cells as well as intermediate and late progenitor cells and thereby stimulate and prolong the phase of active cell proliferation *ex vivo* (emphasis added,). Peled et al assert that effect of Copper and other transition metals depletion could be used for maximizing the *ex vivo* expansion of various types of hematopoietic cells (see page 4, lines 12-18). It is also noted that Peled et al. teaches that method could be practiced with any hematopoietic cell and enrichment of hematopoietic CD34+ cells is only described as a preferred embodiments (see page 5, line 29).

Accordingly, in view of the teachings of Emerson and Peled, it would have been obvious for one of ordinary skill in the art that method of expanding CD34+ cells was recognized as part of ordinary capability of one of skill in the art. One of skill in the art would have been capable of applying this known technique of expanding CD34+ cell, total number of cell and clonability by using the known method of culturing unselected cells as in Emerson et al. The results would have been predictable to one of ordinary skill in the art as Peled has already disclosed that Copper chelator TEPA in presence of low doses of early acting cytokine results in expansion in total number of cell, CD34+ cells and progenitor clonability in short as well as long term culture of bone marrow derived cells (more than 5 weeks, see figure 11 and 22). Therefore, given that copper chelator such as TEPA was available

for use to expand long term culture by inhibiting/delaying the differentiation of CD34+ cells through chelation of transition metal as per teaching of Peled, it would have been obvious for one of ordinary skill in the art to use copper chelator TEPA in the culture medium disclosed by Emerson with reasonable expectation of achieving predictable results of expanding CD34+ cell in culture of MNC. One who would practiced the invention would have had reasonable expectation of success because Emerson had already described a method of *ex vivo* expansion of long term expansion of blood mononuclear cells (MNCs), in presence of early and late acting cytokine, while Peled described use of copper chelator such as TEPA that could facilitate expansion of stem and progenitor cell (CD34+ cells) by inhibiting differentiation of CD34+ cells. Thus, it would have only required routine experimentation to modify the method disclosed by Emerson to include TEPA in the culture medium as required by instant invention. Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 201, 209, 212-214, 239, 244-245 remain rejected under 35 U.S.C. 103(a) and newly added claims 246-248 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al (Sheng Wu Gong Cheng Xue Bao. 2002, 18(3):343-7, abstract) or Emerson et al (US Patent 5,437,994 dated 08/01/1995), Peled et al (WO/1999/40783, 8/19/1999, IDS) and futher in view of Kobari et al (J Hematother Stem Cell Res. 2001; 10(2):273-81).

The teaching of Wang/Emerson and Peled et al have been described above and relied in same manner here. While Wang/Emerson and Peled et al. describe the expansion of CD34+ and CD34+/CD38-hematopoietic stem cells, but differed from claimed invention by not describing expansion of CD133.

However, Kobari et al. teach methods of preparing progenitor or stem cell populations containing stem cells expressing different primitive markers. For

example, a CD133-positive hematopoietic stem and progenitor cells can be expanded in the same manner as the CD34+ subset and conserved its multilineage capacity, which would support the relevance of CD133 for clinical hematopoietic selection (see abstract). Kobari et al teach CD133+ CB cells exhibit the same characteristics as CD34+ CB cells in terms of their ability to proliferate and differentiate into myeloid and lymphoid cells and therefore constitute a new subset of human HSC suitable for use in hematopoietic cell therapy (see page 279, col. 2, para. 3).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the teachings of Wang et al., Peled et al., and Kobari et al. to expand MNC containing hematopoietic stem or progenitor cells expressing $CD34^+$ and/or $CD133^+$ cell surface markers, as a matter of design choice, in the method of culturing and expanding hematopoietic stem or progenitor cells, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. Said design choice amounting to combining prior art elements according to known methods to yield predictable results. One of ordinary skill in the art would be motivated to do so as Kobari et al teach that CD133+ CB cells could be used as an alternative marker that exhibit the same characteristics as CD34+ and is suitable for use in hematopoietic cell therapy (supra). One of skill in the art would have been expected to have a reasonable expectation of success in expanding stem or progenitor cells expressing CD133+ marker because the art teaches the successful selection of HSC using CD133 or CD34+ marker.

It should be noted that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR*, 82 USPQ2d at 1396) (available at http: www. uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Withdrawn-Obviousness Type Double Patenting

Claims 201, 209, 212-214, 239 and 244-245 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2-11, and 23 of copending U.S. patent Application No.: 10/564777 for the reasons of record . It is noted that application '777 has been abandoned. Therefore, rejection is hereby withdrawn.

Double Patenting

Claims 201, 209, 212-214, 244-248 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7-16 of U.S. Patent No. 6,887,704, in view of Peled (WO/1999/40783, 8/19/1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to a method of method of expanding an *ex vivo* population of $CD34^+$, $CD34^+/CD38^-$ and $CD133^+$ hematopoietic stem cells in culture medium, while at the same time inhibiting differentiation of the said cell ex vivo in culture medium; said method comprising:(a) providing hematopoietic mononuclear cells that are not enriched prior to culturing; (b) culturing said mononuclear cells *ex-vivo* for a period of at least 14 days under conditions allowing for cell proliferation, said conditions comprising: (i) providing nutrients and a combination of early acting cytokine or cytokines; (ii) removing one half of the culture volume and replacing it with fresh medium and cytokines weekly; and, at the same time, culturing said mononuclear cells under conditions inhibiting differentiation of said hematopoietic stem cells, said conditions comprising providing an amount of tetraethylenepentamine (TEPA) effective in reducing intracellular available copper concentration in said cells; thereby expanding a

population of said hematopoietic stem cells while at the same time inhibiting differentiation of said hematopoietic stem cells *ex-vivo* for a period of at least 14 days (201, 247-248), wherein the cytokines can be early or late acting cytokines such as TPO, IL-6, SCF, TPO, FLT3 ligand (FL) and granulocyte colony stimulating factor (G-CSF) (claims 212-214), wherein the MNC cells can be derived from bone marrow, peripheral blood, or neonatal umbilical cord blood (claim 209) and wherein TEPA 0.5 to 20 mM (claims 244-245). Claim 246 limits the method of claim 245, wherein said period is greater than 5 weeks. The patent '704 claims recite (i) an expanded undifferentiated hematopoietic cells having reduced intracellular copper content obtained by providing the cells *ex vivo* with conditions for cell proliferation and copper chelator, wherein the combination of chelator and conditions for cell proliferation result in prolonged proliferation, prolonged expansion of clonogenic cells, and maintenance of the undifferentiated state of the cells (claims 1-3), and the cells are derived from neonatal umbilical cord blood (claim 7), the culture medium comprises nutrients and early or late acting cytokines, such as FL and G-CSF (claims 9-13), and the cells are further contain TEPA (claims 14-16). With respect to the limitation of the providing MNC that are unselected, it is noted that MNC from bone marrow contains HSC and '407 teaches providing hematopoietic cell which would contain MNC as evident from the teaching of Peled ('407). Furthermore, at the time the instant invention was made, the prior art taught that copper expansion of CD34+, CD34+/CD38- cells and depopulating the medium to culture the MNC in presence of cytokine are also taught by (Peled WO/1999/40783, 8/19/1999). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use MNC, bone marrow cells to expand CD34+ and CD133+ cells with reasonable expectation of achieving the predictable result. Thus, the instant claims are obvious variants of the patent claims when viewed in light of the teachings of Peled.

Claims 201, 209, 212-214, 244-248 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8,12-14 of U.S. Patent No.7,169,605 (filed as Application No. 10/379,195), in view of Peled WO/1999/40783, 8/19/1999). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to a method of method of expanding an *ex vivo* population of $CD34^+$, $CD34^+/CD38^-$ and $CD133^+$ hematopoietic stem cells in culture medium, while at the same time inhibiting differentiation of the said cell ex vivo in culture medium; said method comprising:(a) providing hematopoietic mononuclear cells that are not enriched prior to culturing; (b) culturing said mononuclear cells *ex-vivo* for a period of at least 14 days under conditions allowing for cell proliferation, said conditions comprising: (i) providing nutrients and a combination of early acting cytokine or cytokines; (ii) removing one half of the culture volume and replacing it with fresh medium and cytokines weekly; and, at the same time, culturing said mononuclear cells under conditions inhibiting differentiation of said hematopoietic stem cells, said conditions comprising providing an amount of tetraethylenepentamine (TEPA) effective in reducing intracellular available copper concentration in said cells; thereby expanding a population of said hematopoietic stem cells while at the same time inhibiting differentiation of said hematopoietic stem cells *ex-vivo* for a period of at least 14 days (201, 247-248), wherein the cytokines can be early or late acting cytokines such as TPO, IL-6, SCF, TPO, FLT3 ligand (FL) and granulocyte colony stimulating factor (G-CSF) (claims 212-214), wherein the MNC cells can be derived from bone marrow, peripheral blood, or neonatal umbilical cord blood (claim 209) and wherein TEPA 0.5 to 20 mM (claims 244-245). Claim 246 limits the method of claim 245, wherein said period is greater than 5 weeks. The patent claims recite a

method of expanding undifferentiated hematopoietic cells ex-vivo, while at the same time inhibiting differentiation of said hematopoietic cells, the method comprising providing said hematopoietic cells ex-vivo with conditions for cell proliferation and, at the same time, with at least one transition metal chelator having an affinity for copper, wherein said chelator and said proliferation conditions result in (i) prolonged active proliferation: (ii) prolonged expansion of clonogenic cells and (iii) maintenance of undifferentiated cells in their undifferentiated state; thereby inhibiting differentiation and expanding said hematopoietic cells ex-vivo (claim 1), wherein the transition metal chelator is tetraethylenepentamine (claim 2). The cells are derived from neonatal umbilical cord blood (claim 8), the culture medium comprises nutrients and early or late acting cytokines, such as FL3 ligand and G-CSF (claims 3-7). Claims12-14 limits the TEPA concentration to 0.1 to 50mM. With respect to the limitation of the providing MNC that are unselected, it is noted that MNC from bone marrow/cod blood contains HSC (CD34+ or CD133+ cells) and '407 teaches providing hematopoietic cell which would contain MNC as evident from the teaching of Peled ('407). Furthermore, at the time the instant invention was made, the prior art taught that copper expansion of CD34+, CD34+/CD38- cells and depopulating the medium to culture the MNC in presence of cytokine are also taught by (Peled WO/1999/40783, 8/19/1999). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to use MNC, bone marrow cells to expand CD34+ and CD133+ cells with reasonable expectation of achieving the predictable result. Thus, the instant claims are obvious variants of the patent claims when viewed in light of the teachings of Peled.

Claims 201, 209, 212-214, 244-248 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S.

Patent No.7,344,881 (filed as Application No. 10/418,639), in view of Peled (WO/1999/40783, 8/19/1999). The rejection is maintained for the reasons of record.

Applicants have indicated that they would consider filing terminal disclaimer upon notice of allowable subject matter in this application.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632